Effect of Polymer Solution Concentration on the Swelling and Mechanical Properties of Glycol Chitosan Superporous Hydrogels

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ABSTRACT: This study examined the effect of the polymer solution concentration on the swelling and mechanical properties of glycol chitosan (GCS) superporous hydrogels (SPHs). GCS SPHs were synthesized using a gas blowing method using glyoxal as the crosslinking agent at different polymer solution concentrations. A small change in the GCS solution concentration resulted in a remarkable change in compression strength and swelling kinetics without any significant loss in equilibrium water imbibing capacity. The increase in mechanical strength accompanied by the decrease in swelling kinetics was caused by the generation of smaller pores during the gelation process of the reactant systems associated with a higher polymer solution viscosity. The apparent diffusion coefficients for a variety of GCS/simulated gastric fluid solution systems were determined from the theoretical fitting of experimental dynamic swelling data, explaining the effects of the solution concentration and crosslinking density on the swelling kinetics. The diffusion coefficients determined in this study are expected to be used as the basic information in estimating the swelling kinetics of samples in different dimension. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 3434–3441, 2010

Key words: hydrogel; swelling; diffusion; crosslink

INTRODUCTION

The gastric retention device is designed to be suspended in the stomach for a long period of time to prolong the release of drugs, minimizing their loss while treating disease, particularly in the gastric environment. Among the many types of devices designed for this purpose, including gastric suspension[1–3] and the muco-adhesive system,[4–6] the superporous hydrogel (SPH) system[7–10] is a promising one. SPH is a three-dimensional network of hydrophilic polymers containing numerous pores on a few to hundreds of micrometers scale diameter and given their large pores, they can absorb significant amounts of environmental water in a short period of time, making them suitable as gastric retention carriers.[11–13]

In this study, glycol chitosan (GCS), a derivative of chitin, was used as the base material for the synthesis of SPH because it possesses biocompatibility, antitoxicity, biodegradability, and a cationic nature to accommodate considerable amounts of water in acidic conditions. Despite such excellent material characteristics, one of the main drawbacks is its unsatisfactory mechanical properties in the highly swollen state, which limits its successful applications to gastric retention devices. Several trials have been carried out to enhance these mechanical properties, namely the synthesis of interpenetrating polymer network (IPN) type hydrogels composed of GCS and other polymeric materials called strengtheners.[14–17] One of the IPN systems recently reported is the GCS/poly(vinyl alcohol) SYSTEM. To establish satisfactory swelling and mechanical properties, a previous study reported the need of 10 h freezing and three heating/thawing cycles.[17] As this lengthy preparation process is barely adaptable to commercial production processes, a new preparation method is required. In this study, homo GCS was used instead of IPN to prepare SPHs with enhanced mechanical strength. As the pore size of the SPHs is expected to be strongly dependent on the aqueous polymer concentration, the SPHs were prepared at different polymer solution concentrations. The effect of polymer solution concentration and the crosslinking density on pore size, structure, and properties including swelling ratio and mechanical properties were investigated.

EXPERIMENTAL

Materials

GCS (DP 2500) and glyoxal (40 wt % aqueous solution, crosslinking agent) were purchased from

Aldrich (Milwaukee, WI). Sodium bicarbonate (Aldrich) was used as a blowing agent and acetic acid (Daejung, Korea) as a pH-adjusting agent.

Preparation of SPHs

The GCS powder was dissolved in distilled water at a concentration ranging from 1 to 4 wt %. To minimize air bubbles, the polymer solution was kept at room temperature without treatment for 24 h. The solution, 5.0 g, was then placed in a glass tube with a 2.0 cm inner diameter and the pH adjusted to 5 with acetic acid. Glyoxal (XX mg) and sodium bicarbonate (40.0 mg) were introduced to the polymer solution with vigorous stirring for a few seconds with the evolution of CO_2 as a result of the reaction between the acid and blowing agent. Neutralization of the reactant system allowed for simultaneous initiation of gelation to produce the SPH. The products were kept at room temperature to allow complete crosslinking, and then freeze-dried. Figure 1 shows this gelation reaction scheme.

Characterization of SPHs

The chemical structure of the SPHs synthesized was identified using Fourier transform infrared spectro-
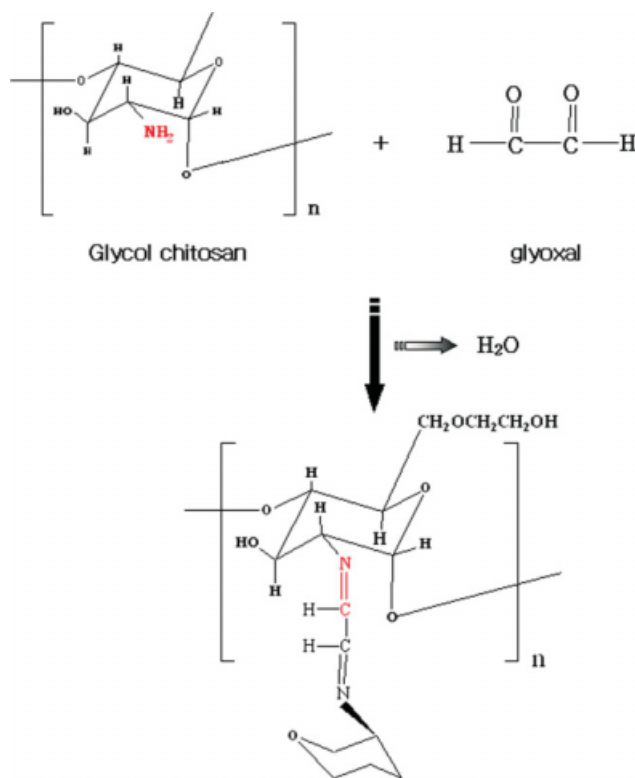
Figure 1 Schematic of the synthesis of the glycol chitosan hydrogel using glyoxal as the crosslinking agent. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

photometer (FTIR, Tensor27, Bruker, Germany). The samples were prepared by crushing the freeze-dried SPHs into a powder and mixing with KBr at a 1 : 100 ratio under high pressure. To examine the swelling behavior of the SPHs, samples with dimensions of 20.0 mm (diameter) × 15.0 mm (length) were prepared. The sample weight was measured periodically until equilibrium was reached where no further weight changes were observed. The same experiments were carried out six times for each sample, and the swelling ratio was determined by the average value. The pH dependence of the swelling capacity was examined by carrying out similar measurements at pH 1.2, 4, and 7, respectively. The swelling ratio was defined using the following equation:

$$Q = \frac{W_t - W_0}{W_0} \tag{1}$$

where W_t and W_0 are the sample weights at time t and the initial stage, respectively.

The viscosity of the polymer solution was measured using a Brookfield viscometer (LVDV-II+ Pro, Brookfield, MA) and determined from an average of six measurements at each concentration.

Scanning electron microscopy (SEM, XL-30 Philips, Netherlands) was used to examine the interior morphology of the prepared SPHs. The dried samples were quenched in liquid nitrogen, fractured, and coated with palladium using an ion coater before each measurement.

The compression strength of the swollen SPH sample was measured four times using a universal tensile machine (Lloyd, England). From that, the average strength was taken.

RESULTS AND DISCUSSION

Chemical identification

The chemical structure of the synthesized GCS SPH was identified by FTIR. The amino peak of the GCS was observed at 1452 cm^{-1}, as shown in Figure 2(a), whereas the imine bond (C=N) produced from the crosslinking between the GCS amino group and the glyoxal aldehyde group via a Schiff base reaction was observed at 1566 cm^{-1} in Figure 2(b).

Swelling properties

SPHs were synthesized at different GCS concentrations of 1, 2, 3, and 4 wt % in solution. The amount of crosslinking agent added to the reactant system ranged from 1 to 5 wt % to that of the GCS for each synthesis, except 1 wt % reactant system. For 1 wt % polymer (reactant) concentration, the amount of crosslinking agent For 1 wt % polymer (reactant)
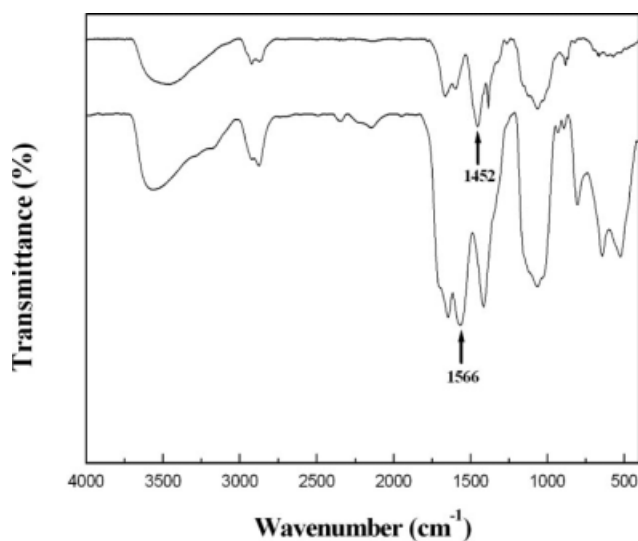
Figure 2 FTIR spectra of glycol chitosan (a) before and (b) after the gelation reaction, respectively.

concentration was adjusted to 4, 8, 12, 16, and 20 wt %, as the gels synthesized at the crosslinker concentration from 1 to 5 wt % were too weak in the swol-

len state to allow measurements of the water uptake. As shown in Figure 3(a), even at such higher crosslinker contents from 4 to 20 wt %, the gels could not sustain their shapes in the highly water swollen state but eventually dissolved in the water, although those were possibly swollen to some degree at the initial stage. For 2 wt % GCS concentration shown in Figure 3(b), the reactant systems with the crosslinker content of 1 and 2 wt % could not produce a tight network structure sufficient to accommodate the high volume of water. The highest water uptake was observed in 3 wt % crosslinker system and above this concentration, the swelling capacity decreased with increasing crosslinking density [Fig. 3(c)]. This trend was similar for the GCS concentration of 4 wt % shown in Figure 3(d). The gels synthesized with 1 wt % crosslinking agent dissolved easily in the simulated gastric fluid (SGF) solution even at the initial stages. However, those synthesized with 3 to 5 wt % of the crosslinker were stable and absorbed high levels of water until reaching equilibrium. This decrease in the equilibrium swelling ratio with increasing crosslinking density is due to the decrease in chain mobility associated with the tight network
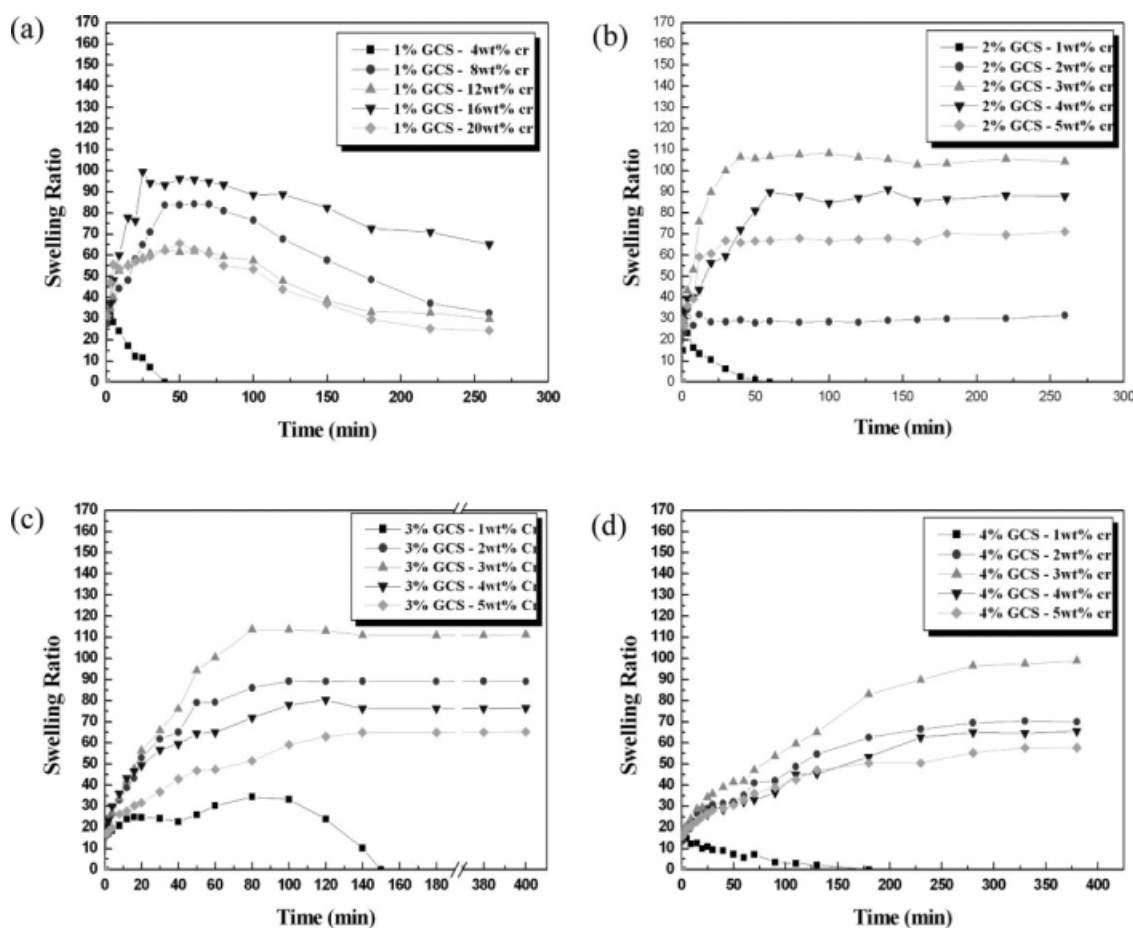
Figure 3 Effect of crosslinking density on the dynamic swelling behavior of glycol chitosan superporous hydrogels prepared at (a) 1, (b) 2, (c) 3, and (d) 4 wt % GCS solution in SGF, respectively.

| Concentration of GCS	Viscosity (cP)
1 wt %	12.0
2 wt %	26.9
3 wt %	96.8
4 wt %	219.4

structure (smaller mesh size). The gel with a 2 wt % crosslinking density had a lower swelling capacity than 3 wt % crosslinker system as its network strength was not as stable as 3 wt % system to maintain their covalent bonds until equilibrium.

The time to reach the equilibrium uptake was quite different for different GCS concentrations. Although 40 min was needed to achieve equilibrium for 2 wt % GCS solution, 80 and 230 min were needed for 3 and 4 wt % samples, respectively. This difference in the time to reach equilibrium was caused by the difference in pore size and the entanglement degree associated with the polymer solution viscosity, which is also significantly affected by polymer concentration in solution, whereby a linear increase in viscosity with solution concentration at the low-concentration range, followed by an abrupt increase from a critical concentration where the molecular entanglements begin to form.[18] At a high-

solution viscosity, the evolution of CO_2 gas bubbles was not as easily detectable as that at a low viscosity, leading to smaller pore sizes. Table I and Figure 4 show the solution concentration dependence of solution viscosity and pore structure, respectively. The pore size decreased with increasing GCS concentration, which resulted in lower equilibrium water uptake. In Figure 4(a), the pore structure of the SPHs prepared in 2 wt % solution was irregular compared with the other systems. The samples prepared at 3 wt % polymer concentration possess regular and large pores to accommodate considerable amount of water. In Figure 4(c), a more obvious difference was observed in which 5 wt % sample possessed much smaller pores than 3 wt % sample due to the higher solution viscosity.

The crosslinking density effect was qualitatively similar to the solution concentration effect. The pore size of 2 wt % crosslinking system was even smaller than that of 3 wt % crosslinking system because some crosslinked bonds were not strong enough to maintain a stable network structure. In Figure 5, higher crosslinking systems resulted in smaller pores due to the tighter network structure.

Figure 6 shows the effect of the crosslinking density on the equilibrium-swelling ratio. This ratio was the highest at 3 wt % crosslinking density, and decreased with increasing crosslinking density from 3 to 5 wt %. Higher water uptake was observed at
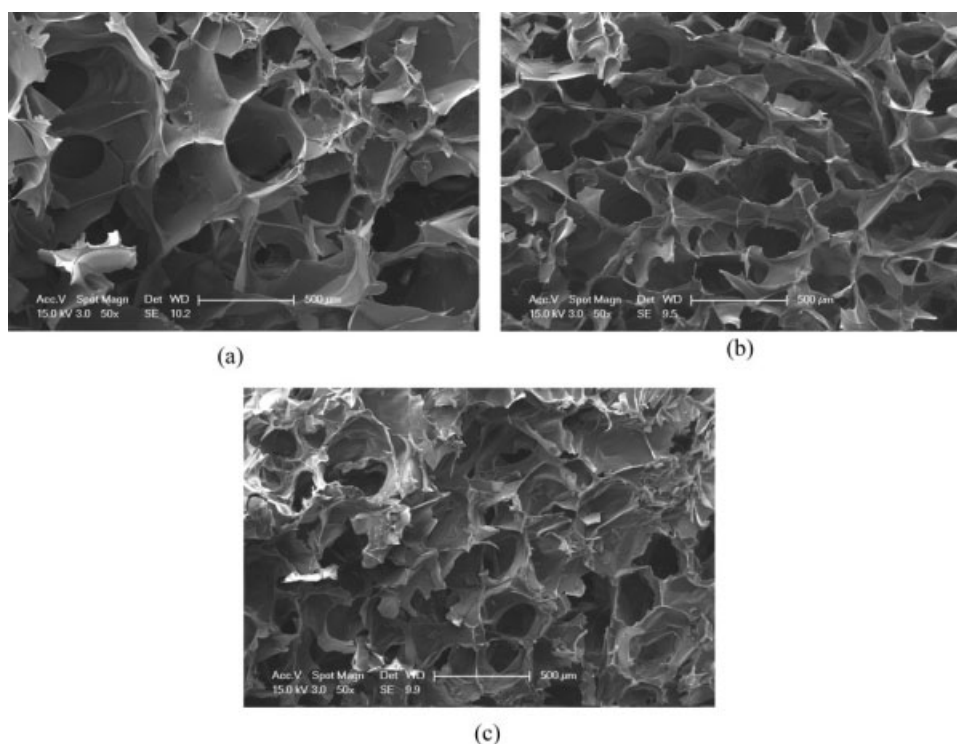
Figure 4 SEM images of glycol chitosan superporous hydrogels prepared at different solution concentrations of (a) 2, (b) 3, and (c) 4 wt %, respectively, at a fixed crosslinking density of 3 wt %.
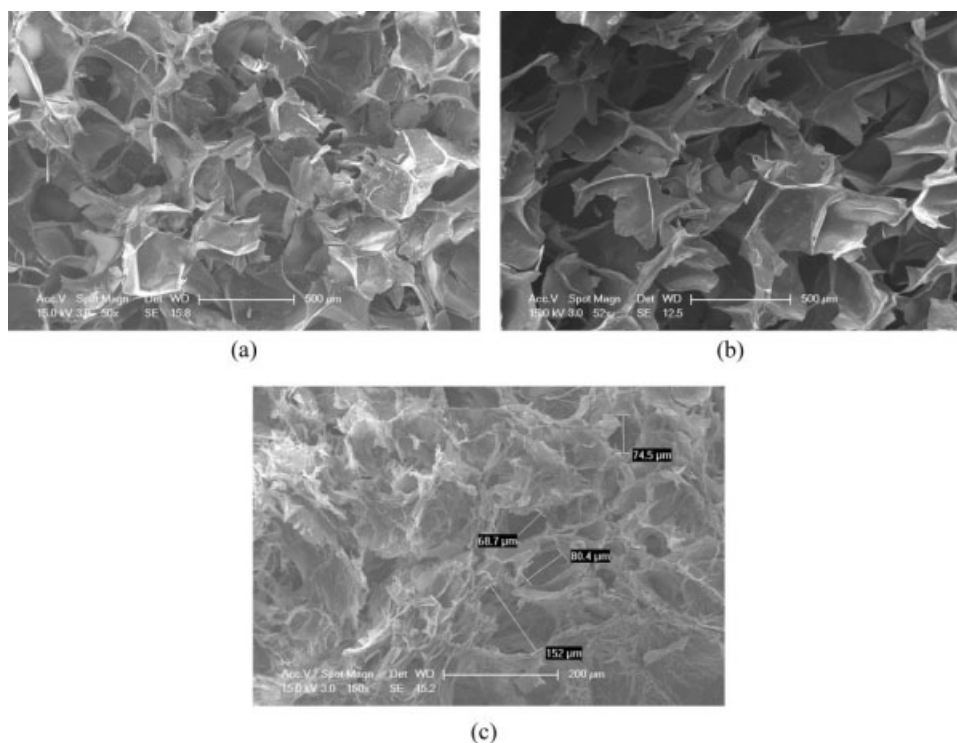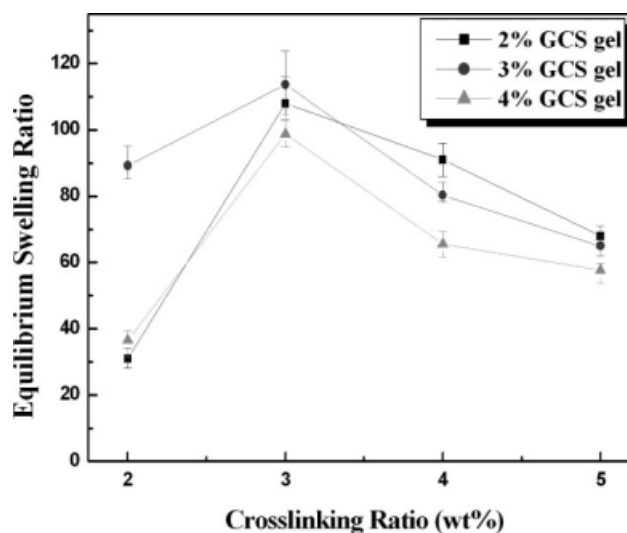
Figure 5 SEM images of glycol chitosan superporous hydrogels prepared at different crosslinker concentrations of (a) 2, (b) 3, and (c) 5 wt %, respectively, at a fixed solution concentration of 3 wt %.

the lower solution concentration due to the solution viscosity effect. The samples with the crosslinking density of 1 and 2 wt % had relatively low-water accommodation abilities as they did not maintain their network stability for enough time to achieve equilibrium.

Mechanical properties

The compression strength was measured for the SPHs swollen up to equilibrium in a SGF solution at 37°C. Figure 7 shows the resulting compression strength and swelling ratio according to the crosslinking density for the hydrogel systems prepared at each solution concentration. The compression strength increased with increasing GCS concentration. The crosslinking density also showed a similar effect on the compression strength but its influence was not as strong as the solution concentration. An inverse relationship was observed between the compression strength and equilibrium swelling ratio due to the plasticization effect. The compression strength of the gels prepared at 2 wt % solution concentration was too weak for application in gastric retention devices, as the minimum criteria of compression strength is 6.86 kP.[19] Indeed, an IPN structure was prepared in a previous study to modify this swelling deficit, enhance the mechanical strength, and obtained improved results. The other samples pre-

pared at 3 and 4 wt % solution might have applications in gastric retention devices from a mechanical point of view. The mechanical strength was improved noticeably by the increase in GCS solution concentration without a significant loss of water imbibing capacity.

Figure 6 Crosslinking density effect on the equilibrium swelling ratio of glycol chitosan superporous hydrogels prepared at different solution concentration.
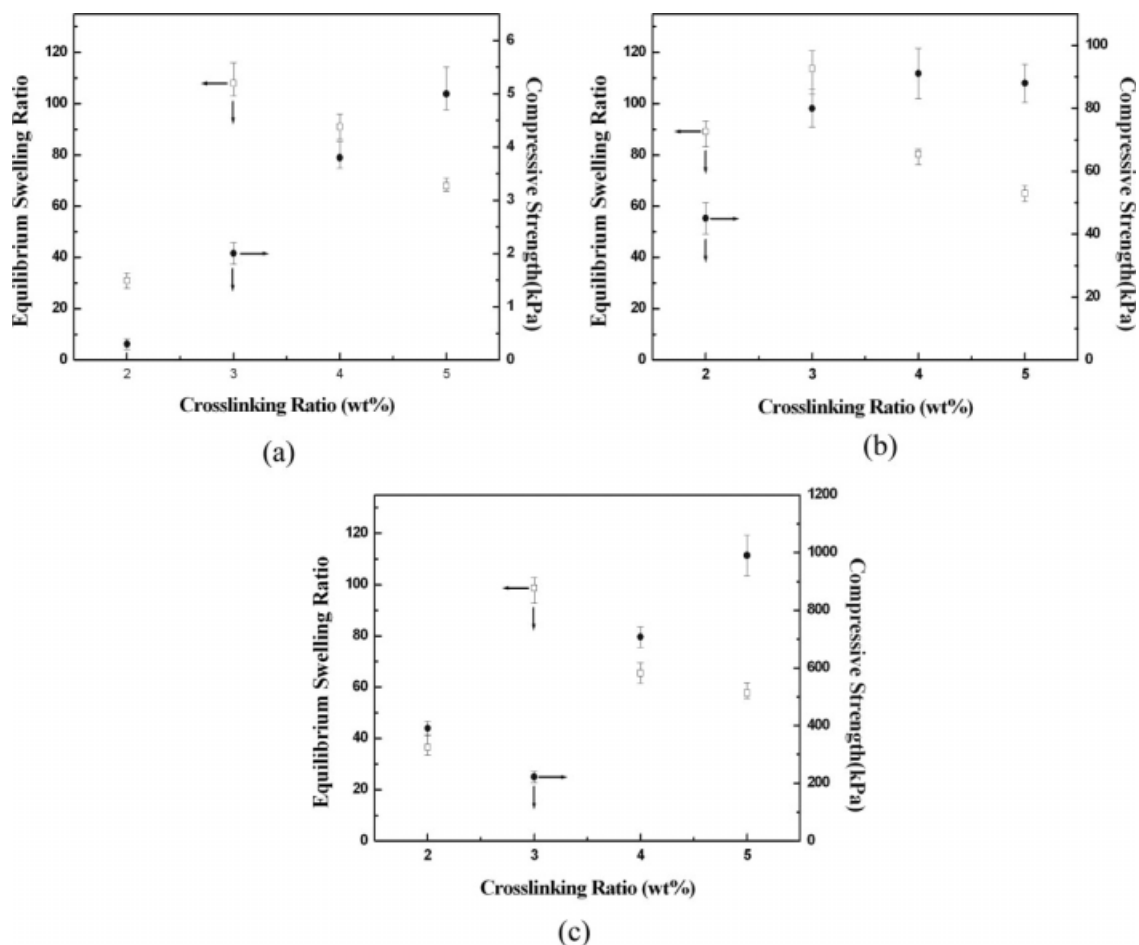
Figure 7 Effect of croslinking density on the equilibrium swelling ratio and mechanical strength of the glycol chitosan superporous hydrogels prepared at (a) 2, (b) 3, (c) 4 wt % GCS solution concentrations.

pH effect

To be applied in gastric retention devices, these polymeric systems need to possess high-swelling capacities at low pH. Figure 8 shows the effect of pH on the hydrogels prepared at a 4 wt % solution concentration. The swelling capacity decreased considerably at lower acidity. No noticeable swelling was observed at neutral conditions, as shown in Figure 8(c). This decrease in swelling capacity was attributed to the cationic nature of the GCS. At a low pH, the polymer chains were ionized to accommodate a considerable amount of water through the osmotic effect.

## Theoretical analysis on swelling kinetics

The swelling kinetics are very important in gastric retention applications as the device should swell fast enough to be suspended in the stomach early enough before passing through the pylorus. The time to equilibrium uptake was shortened simply by preparation of smaller sized samples. Figure 9 compares the swelling kinetics of two samples with different sizes: 20 mm × 15 mm and 20 mm × 5 mm.

The equilibrium time was decreased considerably from 200 to 30 min by reducing the sample thickness from 15 to 5 mm.

The diffusion coefficient is a very useful predictor of swelling kinetics. The diffusion coefficients for the present hydrogels/solution systems were determined from the following analysis. When a solution diffuses into cylindrical gels in three dimensions, eq. (2) can be used to relate the fractional mass uptake and diffusion time when $M_t/M_\infty \leq 0.6$, assuming that the apparent diffusion coefficient involves two diffusion phenomena, bulk and capillary diffusion[20]:

$$
\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{\pi \cdot a^2}\right]^{1/2} - \pi\left[\frac{Dt}{\pi \cdot a^2}\right] - \frac{\pi}{3}\left[\frac{Dt}{\pi \cdot a^2}\right]^{3/2}
$$

$$
+ 4\left[\frac{Dt}{\pi \cdot l^2}\right]^{1/2} - \frac{2a}{l}\left[8\left(\frac{Dt}{\pi \cdot a^2}\right) - 2\pi\left(\frac{Dt}{\pi \cdot a^2}\right)^{3/2}\right.
$$

$$
\left. - \frac{2\pi}{3}\left(\frac{Dt}{\pi \cdot a^2}\right)^2\right] \quad (2)
$$

where M_t and M_∞ are the fractional mass uptakes at times t and infinite time, D is an apparent diffusion
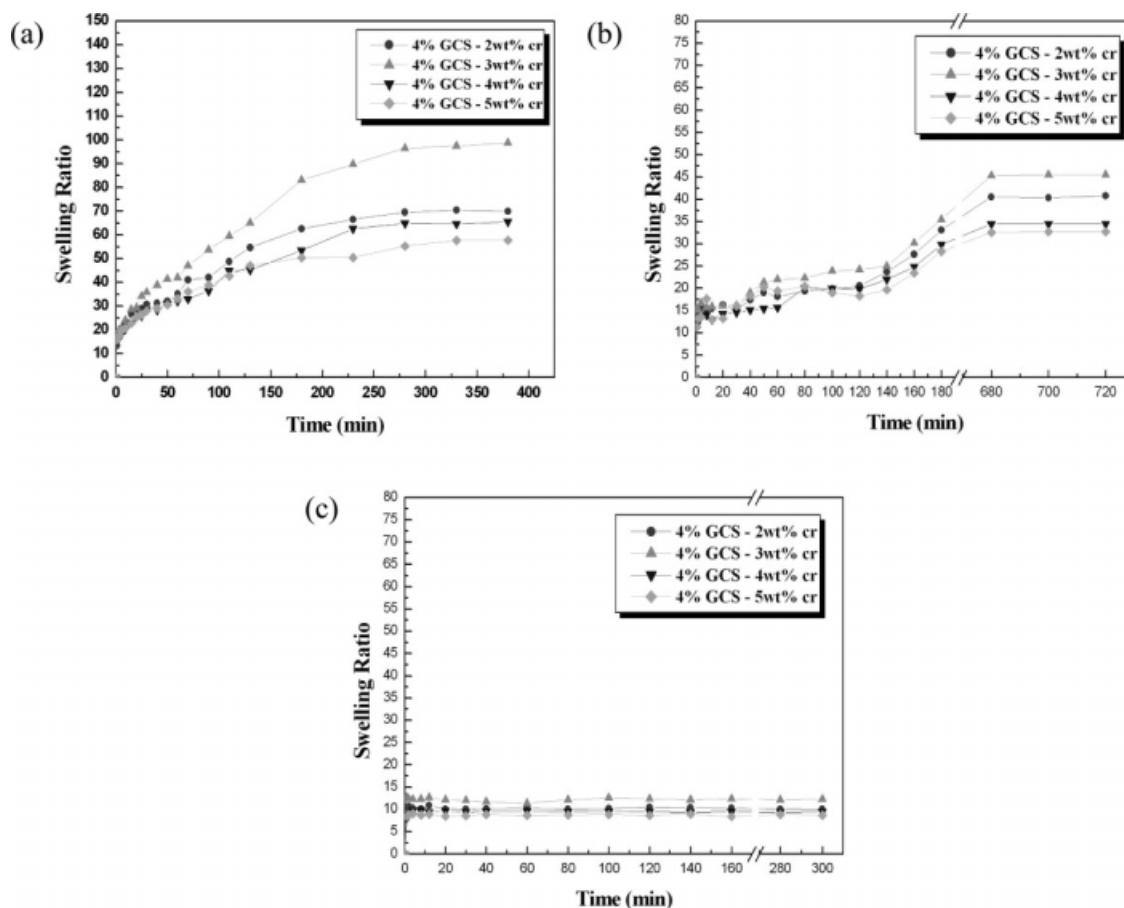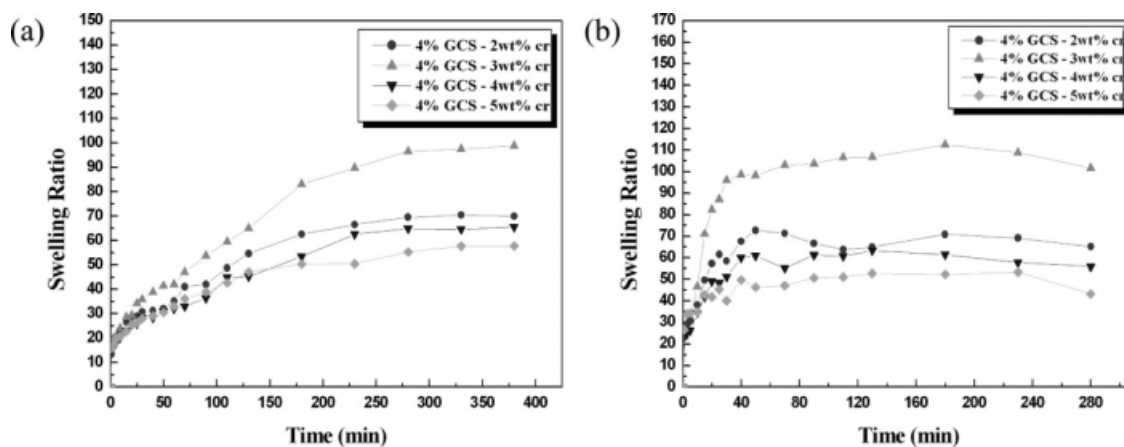
Figure 8 Swelling behavior of the chitosan superporous hydrogels prepared at 2, 3, 4, and 5 wt % crosslinking ratios in (a) SGF, (b) pH 4.0, and (c) pH 7.0 solutions, respectively.

coefficient, t is time, and l and a are the sample thickness and radius, respectively.

In the short-time approximation equation mentioned earlier, the higher order of power terms than a half order of power term are actually negligible.

Therefore, the apparent diffusion coefficient, D, was determined from the curve fitting of M_t/M_∞ versus $t^{1/2}$, as shown in Figure 10. Table II shows the diffusion coefficients of samples with different amounts of crosslinking density prepared at a polymer

Figure 9 Dynamic swelling behavior of glycol chitosan superporous hydrogels with different sizes of (a) 20 mm (ID) × 15 mm (TH) and (b) 20 mm (ID) × 5 mm (TH), respectively.
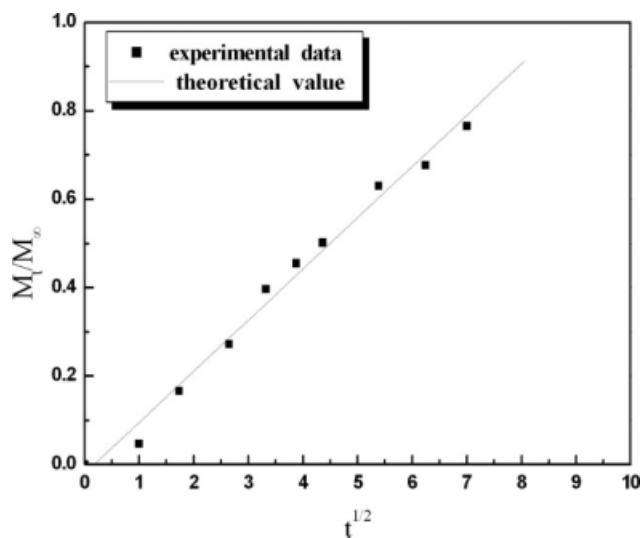
Figure 10 Plot of M_t/M_∞ versus $t^{1/2}$. Experimental data were represented by symbols and theoretical calculation by line (correlation coefficient is 0.994).

solution concentration of 3 and 4 wt %, respectively. The diffusion coefficients were lower at the higher crosslinking density because of lower chain mobility. The diffusion coefficient of 4 wt % sample was much lower than that of 3 wt % sample at a fixed crosslinking density mostly caused by the reduced pore size.

CONCLUSION

GCS SPHs were prepared at different solution concentrations to determine the optimum conditions for both high-swelling capacity and mechanical strength for potential application to gastric retention device. The swelling kinetics and compressive strength were strongly affected by the initial solution concentration but the equilibrium swelling ratio was not. In this study, the preparation of mechanically strong SPHs without any significant loss of water absorption capacity was established by simply changing the initial solution concentration. These SPHs exhibited highly pH sensitive swelling behavior because of their cationic nature. The swelling kinetics could be controlled by the sample dimensions, and the apparent diffusion coefficients were determined from theoretical diffusion analysis. The optimum sample dimension can be predicted for the development of efficient gastric retention devices from the present experimental swelling data and theoretical diffusion

analysis. For this gastric retention application SPHs can be prepared from other polysaccharides by the same synthetic method, once they are hydrophilic and cationic in aqueous state.

TABLE II
Diffusion Coefficient of Glycol Chitosan Superporous Hydrogels Prepared at 3 wt % GCS Solution and 4 wt % GCS Solution in SGF

Crosslinking density	3 wt % GCS solution Diffusion coefficients (cm²/min) $D \times 10^4$	4 wt % GCS solution Diffusion coefficients (cm²/min) $D \times 10^4$
2 wt %	10.17	8.22
3 wt %	8.89	5.67
4 wt %	8.56	5.61
5 wt %	7.59	4.98

References

1. Watanabe, S.; Kayano, M.; Ishino, Y.; Miyao, K. U.S. Pat. 3,976,764, 1976.
2. Sheth, P. R.; Tossounian, J. L. U.S. Pat. 4,140,755, 1979.
3. Mitra, S. B. U.S. Pat. 4,451,260, 1984.
4. Wang, J.; Tabata, Y.; Bi, D.; Morimoto, K. J Controlled Release 2001, 73, 223.
5. Wang, J.; Tauchi, Y.; Deguchi, Y.; Morimoto, K.; Tabata, Y.; Ikada, Y. Drug Delivery 2000, 7, 237.
6. Nagahara, N.; Akiyama, Y.; Nakao, M.; Tada, M.; Kitano, M.; Ogawa, Y. Antimicrob Agents Chemother 1998, 42, 2492.
7. Risbud, M. V.; Hardikar, A. A.; Bhat, S. V.; Bhonde, R. R. J Controlled Release 2000, 68, 23.
8. Sun, Y.; Peng, Y.; Chen, Y.; Shukla, A. J. Adv Drug Delivery Rev 2003, 55, 1201.
9. Simo, C.; Cifuentes, A.; Gallardo, A. J Chromatogr B 2003, 797, 37.
10. Chen, J.; Blevins, W. E.; Park, H.; Park, K. J Controlled Release 2000, 64, 39.
11. Chen, J.; Park, H.; Park, K. J Biomed Mater Res 1999, 44, 53.
12. Chen, J.; Park, H.; Park, K. U.S. Pat. 6,271,278,131, 2001.
13. Klausner, E. A.; Lavy, E.; Friedman, M.; Hoffman, A. J Controlled Release 2003, 90, 143.
14. Qurashi, M. T.; Blair, H. S.; Allen, S. J. J Appl Polym Sci 1992, 46, 255.
15. Miya, M.; Iwamoto, R.; Mima, S. J Polym Sci B 1984, 22, 1149.
16. Ratto, J. A.; Chen, C. C.; Blumstein, R. B. J Appl Polym Sci 1996, 59, 1451.
17. Park, H.; Kim, D. J Biomed Mater Res 2006, 78, 662.
18. Braun, D.; Cherdron, H.; Ritter, H. Polymer Synthesis: Theory and Practice; Springer: Berlin, 2001; p 74.
19. Chen, J.; Park, K. J Controlled Release 2000, 65, 73.
20. Ritger, P. L.; Peppas, N. A. J Controlled Release 1987, 5, 23.